의학석사학위논문

Positive end-expiratory pressure for one-lung ventilation

: a meta-analysis

일측폐 상황에서 호기말양압의 효과

−무작위배정비교임상시험의 메타분석−

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서울대학교 대학원

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원 동 욱

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ABSTRACT

Introduction: Positive end-expiratory pressure (PEEP) is commonly used as a primary intervention for hypoxemia during one-lung ventilation (OLV). However, the effect of PEEP on oxygenation during OLV is controversial. Therefore a systematic review and meta-analysis of randomized controlled trials (RCTs) was performed to investigate the effect of PEEP during OLV.

Methods: Databases including CENTRAL, CINHAL, EMBASE, MEDLINE, SCOPUS, Web of Science, KoreaMed were searched systematically, and finally 7 RCTs with 525 participants were included. The primary outcome was the arterial oxygen partial pressure to fraction of inspired oxygen ratio (P/F ratio) and the secondary outcomes were the lung compliance, dead space to tidal volume ratio (V_D/V_T), shunt fraction, arterial to end-tidal CO_2 partial pressure gradient ($P_{a\text{-}ET}CO_2$ gradient), number of desaturation events during OLV, postoperative radiologic evaluation of lungs and pulmonary function test (PFT) findings. For the primary outcome, a standardized mean difference (SMD) with 95% confidence interval (CI) was calculated and for the secondary outcomes, mean differences (MDs) with 95% CI were calculated. Relevant subgroup analyses were performed to evaluate potential sources of heterogeneity.

Results: The lung compliance improved within and over 30 minutes after onset of OLV but increments were not statistically significant [SMD (95% CI) = 0.50 (-0.10, 1.10), P = 0.10, I^2 = 80% within 30 minutes after OLV, SMD (95% CI) = 0.51 (-0.04, 1.06), P = 0.07, I^2 = 71% over 30 minutes after onset of OLV respectively]. The shunt fraction was significantly lower in the PEEP group compared with the zero end-expiratory pressure (ZEEP) group over 30 minutes after onset of OLV [MD (95% CI) = -5.72 (-7.57, -3.88), $P < 0.001$]. V_D/V_T over 30 minutes after onset of OLV was lower in the PEEP group [SMD (95% CI) = -0.67 (-1.18, -0.16), $P = 0.01$], tendency of decrease in the PEEP group was observed within 30 minutes after onset of OLV but decrement was not statistically insignificant [SMD (95% CI) = -1.14 (-2.38, 0.10), $P = 0.07$]. Results on $P_{a\text{-}ET}CO_2$ gradient were heterogeneous, and there were no statistically significant differences between both groups. Within 30 minutes after onset of OLV, the P/F ratio was lower in the PEEP group though it was not significant [MD (95% CI) = -26.06 (-65.64, 13.53), $P = 0.20$, $I^2 = 86\%$]. Over 30 minutes after onset of OLV, no difference on oxygenation was found between both groups [MD (95% CI) = 11.73 (-19.53, 43.00), $P = 0.46$, $I^2 = 73\%$]. Number of desaturation event which occurred during OLV was not different between two groups [OR (95% CI) = -1.01 (0.43, 2.38), $P = 0.98$, $I^2 = 0\%$], but the pulmonary function test findings were higher in the PEEP group at 72 hours postoperatively. Postoperative atelectasis was not different between both groups.

Conclusion: This meta-analysis suggested that applying PEEP improved shunt fraction and V_D/V_T over 30 minutes after onset of OLV, but improvement of oxygenation was not guaranteed by PEEP. As definite advantages on oxygenation were not found, cautious approach to hypoxemia during OLV should be taken when applying PEEP to dependent lung.

Keywords: Positive pressure ventilation, One-lung ventilation, Thoracic surgery

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ABBREVIATIONS

ARM: Alveolar recruitment maneuver

E_TCO_2: End-tidal CO_2 partial pressure

F_IO_2: Fraction of inspired oxygen

HPV: Hypoxic pulmonary vasoconstriction

MD: Mean difference

OLV: One-lung ventilation

P/F ratio: Arterial oxygen partial pressure to fraction of inspired oxygen ratio

$P_{a\text{-}ET}CO_2$ gradient: Arterial to end-tidal CO_2 partial pressure gradient

PEEP: Positive end-expiratory pressure

$S_{cv}O_2$: Central venous oxygen saturation

SMD: Standardized mean difference

V/Q ratio: Ventilation to perfusion ratio

V_D/V_T: Dead space to tidal volume ratio

ZEEP: Zero end-expiratory pressure

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INTRODUCTION

Atelectasis increases the shunt fraction, worsens the ventilation to perfusion mismatch and deteriorates oxygenation.[1,2] Positive end-expiratory pressure (PEEP) is known to prevent atelectasis caused by general anesthesia.[3] Thus, PEEP has been widely used against hypoxia during general anesthesia and also used as preventive regimen when oxygenation impairment was expected.

One-lung ventilation (OLV) is a ventilatory strategy that ventilates only a part of lungs to facilitate intrathoracic procedures by collapsing the non-ventilated lung. Surgical view and operability in thoracic cage can be improved magnificently with the OLV technique. In spite of its usefulness, there are significant possibilities of desaturation during OLV because only a part of lung is used in oxygenation.[4] As desaturation occurs frequently during OLV, many centers have protocoled strategies against desaturation during OLV, and PEEP has been the most famous primary intervention because PEEP does not interfere OLV and maintains good surgical view. However, there are controversies whether PEEP can solve desaturation during OLV.[5,6] There have been some studies on this subject, but number of RCTs and participants included in those RCTs were small.

Therefore, a systematic review and meta-analysis comparing effects of PEEP and zero end-expiratory pressure (ZEEP) during OLV were designed to see the influences of PEEP on oxygenation, respiratory mechanics, ventilation to perfusion ratio (V/Q ratio) and postoperative outcomes.

METHOD

This systematic review and meta-analysis followed recommendations of Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[7–9]

Search strategy and study selection

Comprehensive search were performed at electronic databases including CENTRAL, CINHAL, EMBASE, MEDLINE, SCOPUS, Web of Science, KoreaMed using searching strategies consisted with keywords such as “one-lung ventilation”, “single-lung ventilation”, “lung separation”, “positive-pressure ventilation”, “positive end-expiratory pressure”, “zero end-expiratory pressure”, “thoracoscopic surgery”, “lung surgery”, and modifications or combinations of these key words. Searching strategies of each database are suggested at appendices at the end of this publication. Other databases including PLOS, DOAJ, LILACS, IMEMR, AIM, SciELO, IndMED, IMSEAR, WPRIM and online registry of clinical trials were also searched (http://clinicaltrials.gov). Abstracts of anesthesia conferences of American, European, and Korean Society of Anesthesiologists from 2000 to 2015 were also reviewed. Finally, references from included studies and relevant review articles were reviewed.

Inclusion and exclusion

RCTs and cross-over studies on effect of PEEP during OLV were included, thus studies on intrathoracic surgeries like lobectomy, mediastinal mass resection which need OLV were included.

Regarding ventilatory strategy, tidal volume should be applied same to both groups to assess true effects of PEEP on respiratory mechanics, V/Q ratio and oxygenation (table 1). The only difference between the intervention and the control groups should be PEEP. Thus, studies with other ventilatory strategies including continuous positive airway pressure, intermittent positive pressure ventilation, and high frequency jet ventilation were excluded because they could affect major outcomes.

There were no limitations in position of patients during operation, type of anesthetic agent used, amount of tidal volume applied during OLV and languages of publications. Non-human trials or duplicated articles were excluded.

Outcomes

The primary outcome was the arterial oxygen partial pressure to fraction of inspired oxygen ratio (P/F ratio) as a gas exchange parameter.

Secondary outcomes were respiratory mechanics like the lung compliance, parameters on V/Q ratio including dead space to tidal volume ratio (V_D/V_T), shunt fraction, arterial to end-tidal CO_2 partial pressure gradient ($P_{a\text{-}ET}CO_2$), vital signs such as heart rate or mean arterial pressure, airway pressures, number of desaturation events during OLV, and postoperative radiologic evaluation or lung function test findings.

Data extraction and items

Two independent reviewers extracted data from full-text of publications. Data suggested in figure without numeric data were extracted by Image processing software (Image J, version 2.1.4.7; NIH, Bethesda, MD, USA).

Extracted data from included studies were publication information and country of studies, number of patients of study groups, demographic data (e.g. age, gender, weight, height and preoperative laboratory results), type of surgery, duration of surgery, duration of OLV, ventilatory strategy, lung compliance, $P_{a\text{-}ET}CO_2$ gradient, V_D/V_T, shunt fraction, P/F ratio, arterial oxygen partial pressure, central venous oxygen saturation ($S_{cv}O_2$) and number of desaturation events during OLV.

For postoperative results, radiologic evaluations of lung at a post-anesthesia care unit and postoperative pulmonary function test data were extracted.

Assessment of risk of bias of included studies

Two independent reviewers assessed the risk of bias by the tool from recommendations of Cochrane Collaboration. Information about random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other source of bias was assessed. Each risk of bias item was ranked as high, low or unclear.

Statistical analysis

Extracted data were processed with the Review Manager software (version 5.3; The Cochrane Collaboration, Oxford, UK). Random-effect models were used for all outcomes because heterogeneity was expected due to differences in ventilation strategies of included studies. When measurement techniques were various, standardized mean difference (SMD) values were used to combine extracted data.

Heterogeneity among the studies was assessed by I^2 statistic and chi-squared test.[10] When there was considerable heterogeneity (I^2 > 50% and P >

0.10 of Chi-squared test), comprehensive explanations were tried by subgroup analysis according to ventilatory strategies (e.g. tidal volume and level of PEEP).

Sensitivity analysis were carried out to check the strength of each study on overall effect by removing each study one by one by predetermined order regarding quality of study and imputed data. Publication bias was evaluated by funnel plot and Egger's test. Asymmetry of funnel plot and the *P* value less than 0.10 by the Egger's test were considered to reflect publication bias.

Result

Search results

From our search strategies, 3173 publications were identified and among them 386 were removed as duplicates. From 2787 publications which were included as primary candidates, 2755 were removed after reviewing titles and abstracts, and 32 were included. By full-text reading, 25 studies were also removed (13 studies due to improper randomization, 9 studies due to inadequate ventilation strategy, 1 study due to lack of important data, 2 abstracts of conference later published in journals). Finally, 7 RCTs including 525 participants were included in our systematic review and meta-analysis (Fig. 1).

Study characteristics

All studies included in our systematic review and meta-analysis was RCTs published between 2003 and 2015. Studies enrolled patients over 18 years old, so there were no pediatric patients.

All RCTs except one used volatile anesthetics as maintenance agent.[11–16] The other study did not suggest specific agent they used to maintain anesthesia.[17] Tidal volumes applied to patients were between 6 to 10 mL/kg. Six studies applied fixed PEEP ranging from 5 to 10 cmH_2O to intervention group.[11–14,16,17] The other study applied individualized PEEP which increased the lung compliance most in each patients and mean PEEP applied during OLV in the intervention group was 6.0 ± 2.0 cmH_2O.[15] Patients received open thoracic surgeries in 3 studies.[13,15,16] In another 2 studies patients received video-assisted thoracoscopic surgeries.[11,12] Other 2 studies did not suggest specific information on approaching techniques of surgeries.[14,17]

In 4 studies OLV was applied while patients were in lateral decubitus position.[12,13,15,16] And in 1 study OLV was applied while patients were in the supine position tilted less than 10 degrees.[11] Remaining 2 studies did not describe position of patients during OLV.[14,17]

One study relieved surgical pain by applying epidural anesthesia from the beginning of anesthesia, but other studies did not apply epidural anesthesia for pain management.[15] Brief summarizations of characteristics of studies were suggested in table 2.

Assessment of risk of bias

Risk of bias was assessed by the tool recommended by the Cochrane Collaboration (Fig. 2 and Fig. 3). Four studies had unclear risk of bias in allocation concealment.[12,14,15,17] Two studies were evaluated to have high risk of other source of bias because these studies lacked important information on methodology.[14,17]

Lung compliance

Five studies (n = 265) reported changes at 0–30 minutes after onset of OLV,[11–13,15,16] and 4 studies (n = 219) reported changes at 30–60 minutes after onset of OLV.[11–13,15]

The lung compliance was higher in the PEEP group compared with the ZEEP group within 30 minutes after onset of OLV though it was not statistically significant [SMD (95% CI) = 0.50 (-0.10, 1.10), P = 0.10, I^2 = 80%, Fig. 4]. The lung compliance was also higher in the PEEP group over 30 minutes after onset of OLV though difference was not statistically significant

[SMD (95% CI) = 0.51 (-0.04, 1.06), P = 0.07, I^2 = 71%, Fig. 4]. Significant heterogeneity was found in the lung compliance within 30 minutes after onset of OLV (I^2 = 80%) and over 30 minutes after onset of OLV (I^2 = 71%). Thus, a subgroup analysis was performed depending on appliance of PEEP during two-lung ventilation (TLV) before changing to OLV. The subgroup to which PEEP was not applied during TLV showed significant increase of lung compliance with no heterogeneity within 30 minutes after onset of OLV [SMD (95% CI) = 0.80 (0.44, 1.16), P < 0.001, I^2 = 36%].[11,12,15,16] Over 30 minutes after onset of OLV, the subgroup to which PEEP was not applied during TLV showed significant increase of lung compliance [SMD (95% CI) = 0.74 (0.29, 1.20), P = 0.001, I^2 = 49%].

Shunt fraction

Only one study mentioned on changes of shunt fraction within 30 minutes after onset of OLV and there was a decrease in the shunt fraction in the PEEP group compared with the ZEEP group though it was not statistically significant [MD (95% CI) = -1.80 (-5.35, 1.75), P = 0.32, Fig. 5].[11]

Two studies reported changes of the shunt fraction over 30 minutes after onset of OLV and shunt fraction decreased significantly in the PEEP group compared with the ZEEP group with no heterogeneity [MD (95% CI) = -5.72 (-7.57, -3.88), P < 0.001, Fig. 5].[11,14]

Dead space to tidal volume ratio

Two studies reported changes of V_D/V_T within and over 30 minutes after onset of OLV.[11,13] There was a tendency of decrease in the PEEP group compared with the ZEEP group within 30 minutes after start of OLV but it was not statistically insignificant [SMD (95% CI) = -1.14 (-2.38, 0.10), P =

0.07, Fig. 6]. A significant decrease of V_D/V_T was observed in the PEEP group compared with the ZEEP group over 30 minutes after onset of OLV [SMD (95% CI) = -0.67 (-1.18, -0.16), P = 0.01, Fig. 6].

Arterial to end-tidal CO_2 partial pressure gradient

Two publications reported changes on $P_{a\text{-}ET}CO_2$ gradient.[11,15] No significant difference between the PEEP group and the ZEEP group was observed in both time intervals (Fig. 7). As directions of change were headed opposite way in each study, results were interpreted separately.

Arterial oxygen partial pressure to fraction of inspired oxygen ratio

Four studies reported on P/F ratio within 30 minutes after onset of OLV,[11,12,13,15] and 5 studies showed results on P/F ratio over 30 minutes after onset of OLV.[11–15]

Within 30 minutes after onset of OLV, P/F ratio of the PEEP group was lower than that of the ZEEP group though it was not statistically significant [MD (95% CI) = -26.06 (-65.64, 13.53), P = 0.20, I^2 = 86%, Fig. 8]. Over 30 minutes after onset of OLV, the PEEP group did not show different P/F ratio compared with the ZEEP group [MD (95% CI) = 11.73 (-19.53, 43.00), P = 0.46, I^2 = 73%, Fig. 8].

Vital signs and airway pressures

Three studies showed results on changes of vital signs by PEEP and ZEEP during OLV.[11,12,14] Results on heart rate and mean arterial pressure were suggested and there were no differences between the PEEP and ZEEP groups.

However airway pressures were significantly higher in the PEEP group compared with the ZEEP group within and over 30 minutes after onset of OLV.[11,12] Effects of PEEP on vital signs and airway pressures were suggested in Fig. 9 and Fig. 10 respectively.

Desaturation event and postoperative outcomes

Two publications reported on desaturation events during OLV and there was no difference between the PEEP and ZEEP groups [OR (95% CI) = 1.01 (0.43, 2.38), P = 0.98, I^2 = 0%, Fig. 11].[12,15] One study showed result on radiologic evaluation of lung at a post-anesthesia care unit and there was no difference between the PEEP and ZEEP group in postoperative atelectasis.[15] Another study reported postoperative pulmonary function test at 72 hours after surgery and higher postoperative pulmonary function test results were observed in the PEEP group.[14]

DISCUSSION

The systematic review and meta-analysis of 7 RCTs including 525 participants was conducted to investigate the effect of PEEP during OLV. This review suggested that there was a possibility that PEEP might improve lung compliance during OLV. The shunt fraction also decreased by PEEP during OLV though decrement was not statistically significant within 30 minutes after onset of OLV. Over 30 minutes after onset of OLV, shunt fraction of the PEEP group was significantly lower than that of the ZEEP group. Statistically significant decrease of V_D/V_T was observed in the PEEP group compared with the ZEEP group over 30 minutes after onset of OLV. Within 30 minutes after onset of OLV, difference was not statistically significant. Even though advantages of PEEP on respiratory mechanics and V/Q ratio were shown, PEEP showed negative influence on oxygenation within 30 minutes after onset of OLV. Negative effects of PEEP were resolved over 30 minutes after onset of OLV though still PEEP did not improve oxygenation.

Increase of compliance

Five studies (n = 265) reported difference in the lung compliance between the PEEP and ZEEP groups within 30 minutes after onset of OLV. [11–13,15,16] Among them, 4 studies (n = 219) reported differences in lung compliance over 30 minutes after onset of OLV.[11–13,15] Analyzing with SMDs, lung compliance was higher in the PEEP group in both time intervals though it was not statistically significant.

A significant heterogeneity was observed within 30 minutes after onset of OLV [SMD (95% CI) = 0.50 (-0.10, 1.10), P = 0.10, I^2 = 80%, Fig. 4] and it was thought to be influenced by ventilatory strategies during TLV before onset of OLV. When a subgroup analysis was done with studies in which PEEP was not applied during TLV, a higher lung compliance was observed in the PEEP group within 30 minutes after onset of OLV [SMD (95% CI) = 0.80 (0.44, 1.16), $P < 0.001$, $I^2 = 36\%$]. On the contrary, in the study which applied PEEP during TLV, the lung compliance was lower in the PEEP group than the ZEEP group.[13] A significant heterogeneity was also found over 30 minutes after onset of OLV [SMD (95% CI) = 0.51 (-0.04, 1.06), $P = 0.07$, $I^2 = 71\%$, Fig. 4]. When same subgroup analysis was done, significantly higher lung compliance in the PEEP group was observed if PEEP was not applied during TLV [SMD (95% CI) = 0.74 (0.29, 1.20), $P = 0.001$, $I^2 = 49\%$].

It is well known that general anesthesia induces large amount of atelectasis with significant decrease in the lung compliance.[18,19] When alveoli collapse, higher pressure named as the critical opening pressure is needed to make collapsed alveoli to inflate again. The critical opening pressure works like threshold, and if an alveolus is inflated over certain volume with the critical opening pressure, from that point inflating that alveolus larger will become easier. As more pressure is needed to inflate atelectatic alveoli as much as non-atelectatic alveoli, atelectasis makes lung compliance decrease. Because it is easier to inflate uncollapsed alveoli than to open and inflate collapsed alveoli, some alveoli which are not collapsed at end-expiratory phase may overdistend. On the contrary, atelectasis decreases with PEEP and as a result compliance increases, and overdistension of alveoli also decreases.

In one included study, authors divided the course of lung inflation into several time sections with same volume intervals.[16] When the lung compliance decreased due to the change from the supine to the lateral decubitus position, most of decreases in lung compliance were observed in the section where lung starts to inflate, and the lung compliance did not decrease after that section. In our meta-analysis, the lung compliance of the PEEP group was higher than that of the ZEEP group though it was not statistically significant. Heterogeneities were found both within and over 30 minutes after onset of OLV. One study showed different results compared with other studies, and ventilatory strategy of that study was different from other studies.[13]

First, the study with different result applied 5 cmH_2O PEEP during TLV after induction of anesthesia and applied relatively high tidal volume during OLV (7–9 mL/kg).[13] PEEP during TLV might have worked as a protective factor to the both groups. High tidal volume applied during OLV might result in auto-PEEP, and make alveoli open in the control group during OLV. PEEP applied during TLV and high tidal volume applied during OLV together might reduce atelectasis of the control group. On the other hand, high tidal volume applied to the PEEP group might cause excessive airway pressure and result in alveolar overdistension.

Except for this study,[13] the lung compliance was significantly higher in the PEEP group. This means properly applied PEEP to the dependent lung can decrease atelectasis and improve respiratory mechanics.

Changes of shunt fraction

PEEP applied during OLV decreased atelectasis and improved mechanical aspect of lung. But it is also important to find how the perfusion of lungs changes during OLV. Two studies (n=132) showed how intrapulmonary shunt changed during OLV by PEEP.[11,14]

One study showed that the shunt fraction was lower in the PEEP group within 30 minutes after onset of OLV though it was not statistically significant [MD (95% CI) = -1.80 (-5.35, 1.75), $P = 0.32$, Fig. 5].[11] Changes of shunt fraction over 30 minutes after start of OLV were suggested in 2 studies and significant decrease of shunt fraction was observed in the PEEP group [MD (95% CI) = -5.72 (-7.57, -3.88), $P < 0.001$, Fig. 5].[11,14]

The shunt fraction means ratio of blood flow that does not participate in gas exchange, that is, ratio of perfusion without ventilation. Shunt fractions of awake healthy adults are usually negligible.[20] However, immediately after induction of general anesthesia and start of controlled ventilation, atelectasis starts to occur and blood flow that perfuses collapsed alveoli becomes shunt.[18,19] Deoxygenated systemic venous blood that flows into the left atrium via shunt contaminates oxygenated pulmonary venous blood and causes systemic hypoxemia. Thus, if PEEP decreases atelectasis during TLV, it can decrease shunt and improve oxygenation. However, shunt during OLV is more complex than that of TLV.

OLV inevitably creates large quantity of intrapulmonary shunt by discontinuing ventilation of unilateral lung and collapsing it. When the intra-alveolar oxygen partial pressure decreases, precapillary vasoconstriction supplying hypoxic alveoli restricts blood supply to shunt. This protective mechanism is called hypoxic pulmonary vasoconstriction (HPV) and facilitates OLV. HPV improves ventilation to perfusion mismatch of whole lung by decreasing perfusion of hypoxic alveoli and redirecting perfusion to alveoli which are rich of oxygen. Even though interindividual variability of HPV is wide, HPV can decrease perfusion of the non-ventilated lung by 50%.[21] The problem is that HPV can be weakened by increased airway pressure and pulmonary vascular resistance, which can occur with PEEP. Thus, whether PEEP will be advantageous or not in respect of shunt fraction will be decided by sum of shunt induced by atelectasis which will be decreased by PEEP and shunt induced by decrease of HPV which will be attenuated by PEEP, but it will be difficult to estimate results due to interindividual variability. In one study, shunt fraction decreased though it was not significant,[11] in another study shunt fraction decreased significantly over 30 minutes after onset of OLV.[14] Ventilatory strategies of two studies were very similar, but position of patient was different, the supine position in one study,[11] the lateral decubitus position in another study.[15] It is known that the lateral decubitus position during OLV is advantageous regarding intrapulmonary shunt. In the lateral position, perfusion prefers the dependent lung due to the effect of gravity and as a result, shunts decrease.[22]

Decrease of dead space

Two studies (n = 134) reported differences of V_D/V_T between the PEEP and ZEEP groups.[11,13] V_D/V_T showed tendency of decrease within 30 minutes after onset of OLV in the PEEP group [SMD (95% CI) = -1.14 (-2.38, 0.10), *P* = 0.07] and significantly decreased in the PEEP group over 30 minutes after onset of OLV compared with the ZEEP group [SMD (95% CI) = -0.67 (-1.18, -0.16), *P* = 0.01].

Dead space means a part of tidal volume that 'does not participate in gas exchange' and represents 'wasted ventilation'.[11,13] Physiologic dead space is calculated by Bohr equation and it is composed of anatomical dead space, alveolar dead space and shunt dead space. Anatomical dead space is formed with conducting airways. Alveolar dead space arises from alveolar overdistension and shunt dead space is created by right to left shunt and its resultant $P_{a\text{-}ET}CO_2$ increase.[23]

The anatomical dead space is an actual space that can be defined anatomically and is known to be noncompliant.[24] However, the alveolar dead space is a functional space that reflects efficiency of gas exchange and the shunt dead space is a fictitious space that shows efficiency of pulmonary perfusion. Every situation which interferes CO_2 exchange (e.g. decrease of cardiac output, increase of atelectasis or formation of shunt) increases alveolar and shunt dead space. PEEP decreases atelectasis, makes alveolar re-expansion easier and thus decreases alveolar overdistension. As a result, more perfusion is exposed to alveolar–capillary interface and efficiency of gas exchange increases. By this mechanism, PEEP helps to decrease alveolar dead space. PEEP also decreases shunt fraction. As intrapulmonary shunt decreases, $P_{a\text{-}ET}CO_2$ gradient also decreases, that is, shunt dead space decreases.

In our meta-analysis, dead space was observed to decrease in the PEEP group compared with the ZEEP group. One study reported measured values of physiologic dead space.[13] As anatomical dead space is noncompliant, changes of physiologic dead space might be interpreted as changes of alveolar and shunt dead space. Results of another study were values calculated by Hardman–Aitkenhead equation showed significant decrease of dead space,[11] and this equation estimates alveolar dead space.[25] This can be interpreted that PEEP decreased alveolar overdistension and improved efficiency of gas exchange.

Changes of $P_{a\text{-}ET}CO_2$ gradient

Two studies (n = 142) showed results on $P_{a\text{-}ET}CO_2$ gradient.[11,15] In both time intervals no statistically significant results were observed because of significant heterogeneity. In one study, $P_{a\text{-}ET}CO_2$ gradient decreased in the PEEP group,[11] on the contrary, in another study $P_{a\text{-}ET}CO_2$ gradient decreased in the ZEEP group.[15]

$P_{a\text{-}ET}CO_2$ gradient is the difference between arterial CO_2 partial pressure and end-tidal CO_2 partial pressure (E_TCO_2) and reflects physiologic dead space. In an ideal alveolus which has no dead space, $P_{a\text{-}ET}CO_2$ gradient is zero because arterial and alveolar CO_2 partial pressure are equal. However, if there is either anatomical or alveolar dead space, pulmonary arterial CO_2 will be excreted to only a portion of tidal volume, and exhaled CO_2 in alveolar air will be diluted by room air from the dead space. As a result, $P_{a\text{-}ET}CO_2$ gradient is increased.

In one study, $P_{a\text{-}ET}CO_2$ gradient decreased in the PEEP group because the dead space decreased.[11] But in another study, $P_{a\text{-}ET}CO_2$ gradient was higher in the PEEP group compared with the ZEEP group and this means the increase of dead space.[15] The different directions of the PEEP effect were thought to be come from different ventilatory strategies of these studies.

One study applied tidal volume as much as 9 mL/kg and 1:1 inspiration to expiration ratio during OLV.[15] Alveolar overdistension due to high tidal volume and short expiration time might have decreased benefits of PEEP. And shunt dead space might be increased due to increase of intrathoracic pressure and airway pressures which attenuated HPV and increased intrapulmonary shunt. PEEP might change distribution of pulmonary blood flow, and as perfusion to overdistended alveoli decreased, ratio of high V/Q region increased even more, which resulted in increase of dead space and decrease of ventilatory efficiency.[15]

Changes in oxygenation

Four studies (n = 219) reported P/F ratio within 30 minutes after onset of OLV,[11–13,15] and 5 studies reported P/F ratio over 30 minutes after onset of

OLV.[11–15]

Within 30 minutes after onset of OLV, the P/F ratio was lower in the PEEP group though difference was not statistically significant [MD (95% CI) = -26.06 (-65.64, 13.53), P = 0.20, I^2 = 86%]. Over 30 minutes after onset of OLV, there was no difference between both groups [MD (95% CI) = 11.73 (-19.53, 43.00), P = 0.46, I^2 = 73%].

P/F ratio means ratio of arterial oxygen partial pressure and fraction of inspired oxygen (F_IO_2), and reflects oxygenation dysfunction. Not only respiratory mechanics but also many factors including diffusion limitation, hypoventilation, hemodynamic factors affect oxygenation.[26] Thus, improvement of respiratory mechanics or V/Q ratio do not necessarily lead to improvement of oxygenation directly.

Most concerning pitfall of PEEP during OLV must be attenuation of HPV. When alveolar oxygen partial pressure decreases, vasoconstriction of pulmonary arterioles to non-ventilated alveoli occur and blood flow is redistributed to well ventilated alveoli, and as a result V/Q ratio improves. When PEEP increases airway pressure, HPV is attenuated and blood flow to the non-ventilated lung may increase. Interindividual variability of HPV is wide and influence of PEEP on shunt during OLV is difficult to estimate. Shunt may decrease if atelectasis decreases more than HPV is attenuated. But PEEP may still have negative effect on oxygenation if $S_{cv}O_2$ is decreased by changes of cardiac output and oxygen delivery. In one included study, $S_{cv}O_2$ was lower in the PEEP group within 30 minutes after onset of OLV though it was not statistically significant, and was significantly lower in the PEEP group over 30 minutes after onset of OLV.[11]

Intrathoracic pressure may be less influenced in thoracotomy surgeries compared with video-assisted thoracoscopic surgeries.[27] But there is still a possibility of cardiac output to be decreased. First, cardiac output may decrease due to increased right ventricular afterload by increased pulmonary vascular resistance. In addition, increased vagal tone induced by increased airway pressure can decrease cardiac output.[28] There were several studies with conflicting results on this issue. In one study, cardiac output was increased when PEEP was applied as much as intrinsic PEEP during OLV, but when 5 cmH_2O PEEP was added more, cardiac output was decreased significantly.[29] In another study, cardiac output of the PEEP group showed no difference compared with the ZEEP group during OLV while upper lung was collapsed. However, when the upper lung was insufflated with oxygen at 10 cmH_2O pressure, cardiac output of the PEEP group was lower than that of the ZEEP group.[27]

In our meta-analysis, oxygenation was lower in the PEEP group within 30 minutes after onset of OLV though it was not statistically significant. This tendency was prominent in studies which applied high tidal volume during OLV.[13,15] Onset of HPV is rapid, thus HPV starts to increase immediately after OLV. But it is not until 20–30 minutes have passed from start of OLV that HPV reaches to plateau. Thus, if PEEP and high tidal volume were applied while HPV had not reached to plateau yet, HPV might have been weakened due to increase of airway pressure and effect of shunt on oxygenation might be exaggerated. Actually, in our meta-analysis, airway pressure was significantly higher in the PEEP group (Fig. 10). And increased intrathoracic pressure and pulmonary vascular resistance due to high tidal volume could decrease cardiac output and $S_{cv}O_2$, and resulted in negative effect on oxygenation.

Over 30 minutes after onset of OLV, negative effect of PEEP on oxygenation disappeared. This change was thought to be provided by stabilization of HPV. HPV occurs immediately after start of OLV, reaches to plateau after 20–30 minutes and plateau lasts about 40 minutes. After the plateau ends, HPV increases again and reaches to peak in several hours. Thus, in included studies, HPV should had been reached to plateau over 30 minutes after onset of OLV. As a result, disadvantages of PEEP might be minimized while advantages of PEEP were maximized due to decrease of atelectasis. Previously, significant decrease of shunt over 30 minutes after onset of OLV was observed.

One study suggested number of patients with arterial oxygen partial pressure over 60 mmHg in each group.[17] In this study, PEEP applied from TLV resulted in less hypoxemia when OLV was over.

In conclusion, on the contrary that PEEP improved respiratory mechanics and V/Q ratio, PEEP during OLV did not improve oxygenation. Before HPV reached to plateau, PEEP might cause disadvantage on oxygenation, but this situation improved over 30 minutes after onset of OLV. One study showed decrease of oxygenation in the PEEP group but showed no difference between the PEEP and ZEEP groups in respect of intraoperative desaturation events.[15] This suggests that effect of PEEP on oxygenation cannot be directly connected to effect on hypoxemia.

Postoperative outcomes

Repeated collapse and re-expansion of atelectatic alveoli causes lung injury by shearing stress. This injury can cause alveolar necrosis, increase of capillary permeability, inflammatory responses. Some alveoli can get volutrauma due to overdistension. If PEEP can decrease lung injury by reducing atelectasis, it can make differences in postoperative outcomes—hospital stay, major and minor complications, morbidity and mortality.

Some of included studies suggested postoperative outcomes besides intraoperative outcomes. In one study, reviewing radiographic evaluation at the post-anesthesia care unit revealed no differences in postoperative lung complications between the PEEP and ZEEP groups.[15]

Another study suggested postoperative pulmonary function test findings at 72 hours after operation.[14] In this study, the PEEP group showed better postoperative pulmonary function status compared with the ZEEP group. Results of this study showed short-term benefits of PEEP on postoperative pulmonary function but still lacked long-term perspectives.

Limitations

In this systematic review and meta-analysis, definite improvement of V/Q ratio were observed over 30 minutes after onset of OLV and the possibility of improvement of respiratory mechanics and still vague effect on oxygenation were also reported. However, there are some limitations that have to be discussed.

First, many studies applied high tidal volume during OLV. Even though high tidal volume decreases atelectasis, it can induce direct volume injury. Also it can reduce benefits of PEEP by increasing intrathoracic and airway pressure. Increased airway pressure can deteriorate HPV and worsen intrapulmonary shunt. As previously mentioned, high tidal volume can decrease $S_{cv}O_2$ and cause negative effect on oxygenation. That is, maximal advantages of PEEP cannot be expected with high tidal volume ventilation during OLV.

Another limitation is anesthetic agents used for maintenance of anesthesia. Volatile anesthetics above 1 minimal alveolar concentration is known to inhibit HPV and most of studies included in our meta-analysis used volatile anesthetics as a maintenance agent.[30] Though it is known that modern volatile anesthetics below 1 minimal alveolar concentration do not induce relevant inhibition of HPV, some studies used volatile anesthetics above 1 minimal alveolar concentration, and this also can offset advantages of HPV.[31]

Many studies used high F_IO_2 to prevent desaturation during OLV, but high concentration of O_2 can cause absorption atelectasis and airway closure. Nitrogen of mixed air can work as alveolar splint at end-expiratory phase and lowering F_IO_2 can be helpful to prevent atelectasis. However, lowering F_IO_2 can be challenging for anesthesiologists because even 80% of F_IO_2 dramatically decreases apneic time interval to desaturation.[32]

PEEP is also known to be maximally effective with alveolar recruitment maneuver (ARM), but ARM was not applied in most included studies.[33] To make collapsed alveoli open, peak inspiratory pressure above 30 cmH_2O is needed, and complete reversal of atelectasis requires prolonged period of considerably high pressure over 40 cmH_2O.[34] Thus, atelectatic alveoli might not be inflated solely by PEEP, and applying PEEP alone could even induce paradoxical increase of pulmonary vascular resistance. Resultant increase of shunt may decrease oxygenation.[11] In one study, process which authors called 'normalization'—3 consecutive ventilations by 45 cmH_2O airway pressure—was applied in both groups before applying OLV and increase of oxygenation was observed after 20 minutes of OLV in the PEEP group.[16] In another study, ARM was applied before OLV and improved oxygenation was observed in the PEEP group after re-establishment of TLV.[11] In this respect, to see the true effect of PEEP, ARM had to be applied before applying PEEP.

Lastly, number of RCTs included in our systematic review and meta-analysis were small, and power of study was limited. Therefore, many results without significance might be due to the lack of power.

Oxygenation is complex process and respiratory mechanics only constitute a part of this process. In our meta-analysis, PEEP improved respiratory mechanics and V/Q ratio, but in order to evaluate the effect of PEEP on oxygenation, more studies controlling other variables are needed.

First, ventilation design should include ARM before applying PEEP to maximize the effect of PEEP. Protective strategy should be considered to minimize the effect of tidal volume on airway pressure and HPV. Also total intravenous anesthesia should be considered instead of inhalation anesthesia not to impede the effect of HPV. Long term outcome should be observed in addition to intraoperative outcome. If PEEP can make benefits to patients, PEEP should be applied to patient even when PEEP does not improve oxygenation. For example, protective ventilation is known to decrease inflammatory response during OLV,[35] though decrease of inflammatory marker did not always result in clinical benefit.[36]

CONCLUSION

PEEP is known to improve respiratory mechanics, V/Q ratio and oxygenation during TLV, but advantage of PEEP during OLV has been controversial. In our systematic review and meta-analysis, PEEP improved V_D/V_T and shunt fraction over 30 minutes after onset of OLV but improvement did not result in increase of oxygenation. It was partially because ventilatory strategies that attenuated advantages of PEEP, but partially because of diversity of various factors involved in oxygenation.

There are many causes of desaturation. Though PEEP has been used as one of the primary interventions against desaturation during OLV, there are little evidence that PEEP improves oxygenation during OLV. Status of patients and pathophysiology of desaturation should be considered first, and then careful judgement is required for whether or not PEEP would help patients on oxygenation. Indiscriminate use of PEEP should be avoided.

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TABLES

Table 1. Inclusion and exclusion criteria

Types of surgery	Randomized controlled trials
	No region or language limitation
Types of participants	Patients receiving intrathoracic surgery which requires one-lung ventilation
	No age limitation
Types of intervention	Positive-end expiratory pressure
Types of ventilation	Common ventilatory strategy
	Exclusion: Ventilatory strategy that affects oxygenation. e.g. continuous positive airway pressure
Types of outcome	**Primary outcome**
	Oxygenation : P/F ratio
	Secondary outcomes
	Respiratory mechanics : Lung compliance
	V_D/V_T
	shunt fraction
	$P_{a-ET}CO_2$ gradient
	Desaturation events
	Radiologic evaluation at the post-anesthesia care unit
	Postoperative pulmonary function test results

Table 2. Characteristics of studies

Study ID	Interventions in each arm	AGE (yr)	Wt/ *BMI*	sex M/F	FEV1 or FEV1%	duration of surgery	duration of OLV	Type of surgery	open/VATS op.position	Ventilation TLV TV	bitween TLV & OLV	Ventilation OLV TV/mode	Maintenance drugs	Language	Country
Valenza 2004	1. PEEP 10cmH2O	62+8	*25.3+3*		78.9+17			thoracic surgery (33 lobe resection & 7 pneumonectomy)	open/ lateral	TV 10mg/kg (mode unkn), insp time 33%, RR은 환자의 정상 PaCO2유지하도록, ZEEP, FiO2 60%	normalization before randomization 45cmH2O로 3회 ventilation		ISO (1.5 maximal allowed concentration) + FTN 50ncg bolus	eng	Italy
	2. ZEEP	64+9	*24.3+4*		78.9+23										
Leong 2007	1. PEEP 5cmH2O	66+8.1	71+13.1	8/3	2.05+0.54	2:33+1:01	1:52+0:48	lung resection	open/ lateral	PCV(TV 7-9ml/kg), 5cmH2O PEEP, i:e = 1:2, RR=EtCO2 4.5-5.5kPa (34-41mmHg)		PCV(TV 7-9ml/kg), i:e=1:2, FiO2 1.0	ISO	eng	UK
	2. PEEP 8cm H2O	62+5.1	72+15.7	7/4	2.43+0.69	1:55+0:33	1:38+0:32								
	3. PEEP 10cm H2O	68+7.1	78+17.6	5/5	1.78+0.73	2:22+1:05	1:48+0:40								
	4. ZEEP	64+9.1	72+10.2	7/3	1.93+0.57	2:11+0:53	1:53+0:57								
Mascotto 2003	1. Patient-specific PEEP (4.3 ± 2cmH2O)	63+10	70+13	19/9	2.233+0.578	212+74(min) =3:32+1:14	x	pneumonectomy, lobectomy, atypical lung resection	open/ lateral	9ml/kg, i:e=1:1, insp pause 10%		9ml/kg	ISO	eng	Italy
	2. ZEEP	64+8	71+12	18/4	2.536+0.766	197+84 = 3:17+1:24	x								
Choi 2015	1. PEEP 8cmH2O	49+14	*22.7+2.5*	6/25	97+17	1:23+0:48	1:00+0:33		VATS/ supine (tilting <10')	8ml/kg VCV, i:e = 1:2, insp pause 10%, RR 12 in FiO2 with ZEEP	position후 PCV로 전환, PEEP/ AR+ PEEP 적용. AR: PIP/PEEP 30/10(5회)> 35/15(5회)> 40/20(10회) & i:e=1:1	6ml/kg VCV	SEVO(1.0-2.0%) + rFTN (0.1-0.3 mcg/kg/min)	eng	ROK
	2. PEEP 8cm H2O + AR	46+14	*23.0+3.3*	13/17	99+17	1:35+0:37	1:14+0:29								
	3. ZEEP	44+14	*23.3+3.0*	9/22	106+14	1:22+0:42	1:07+0:39								
Kim 2012	1. low TV(6ml/kg)	28.4+13.9	60.7+4.7	17/3		1:01.6+0:19		Rt. WR	VATS/ lateral	10ml/kg PBW		6ml/kg VCV	DES	eng	ROK
	2. low TV(6ml/kg) + PEEP 5cmH2O	35.3+17.1	62.6+7.8	18/2		1:04.2+0:21.4						6ml/kg VCV			
	3. high TV(10ml/kg)	34+18.1	60.1+7.5	18/2		1:09.8+0:09.8						10ml/kg VCV			
Razzaque 2012	1. PEEP 5cmH2O	41.59+1.9								TV 7-9ml/kg, Pr-regulated VCV, i:e=1:2		TV 7-9ml/kg, Pr-regulated VCV, i:e=1:2		eng	Pakistan
	2. ZEEP	43.17+1.4													
Pei-yan 2011	1. 6ml/kg+ PEEP 5cmH2O	25-69	68.7 ± 10.1					pulmonary lobectomy	open	10ml/kg, i:e= 1:2		6ml/kg VCV	ISO, TIVA?	chinese	china
	2. 6ml/kg+ ZEEP														

FIGURES

Figure 1. PRISMA diagram

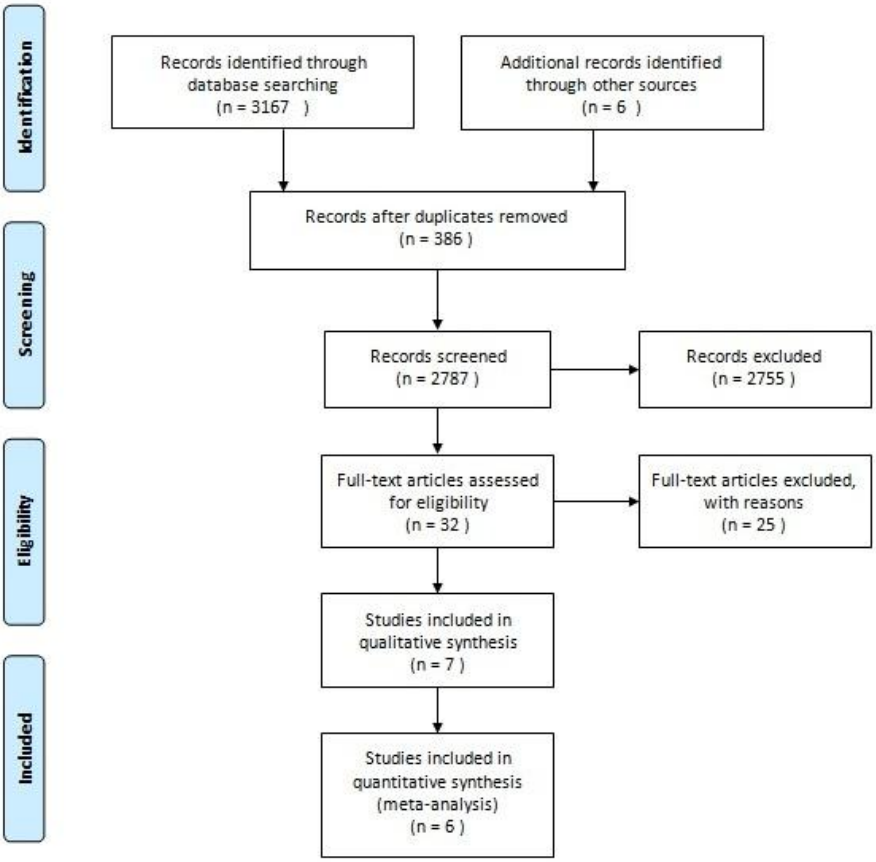


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Plus sign in green circle means low risk of bias. Question mark in yellow circle means unclear risk of bias. Minus means high risk.

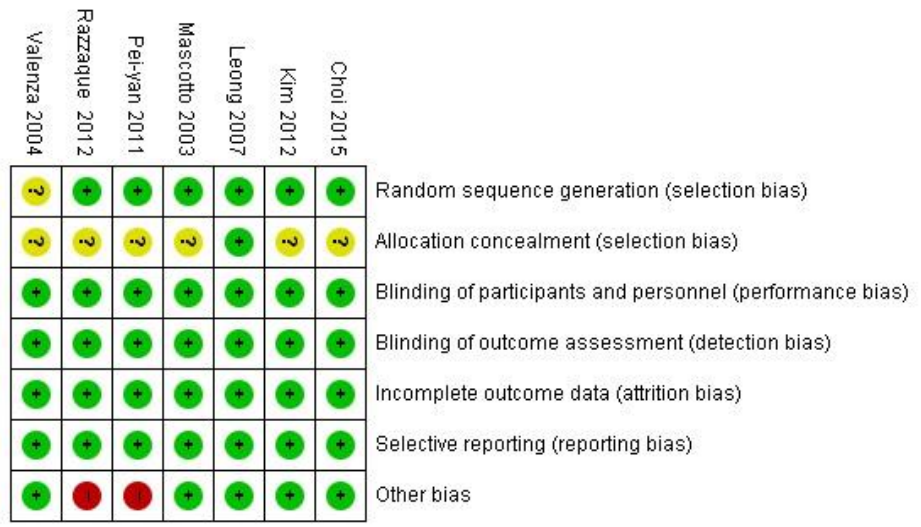


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

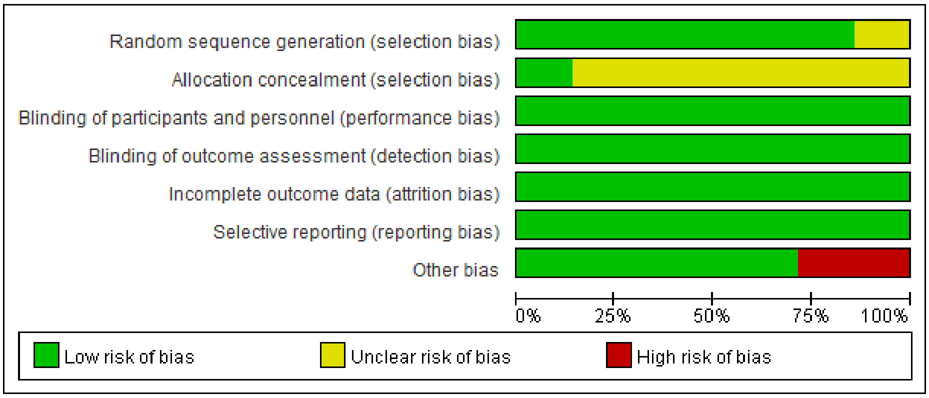


Figure 4. Lung compliance within or over 30 min after onset of OLV

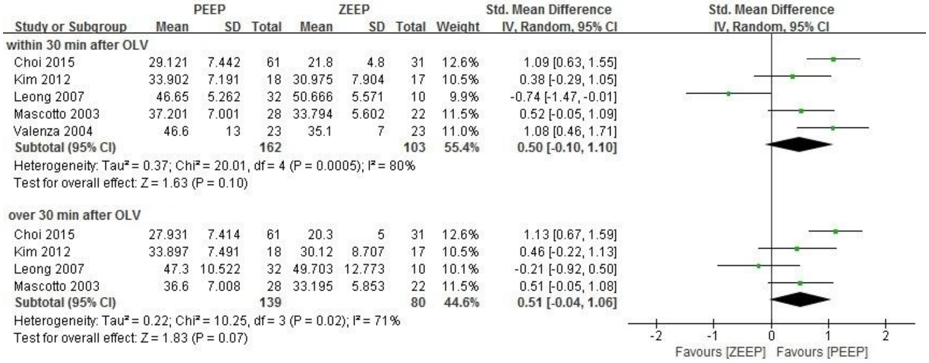


Figure 5. Shunt fraction within or over 30 min after onset of OLV

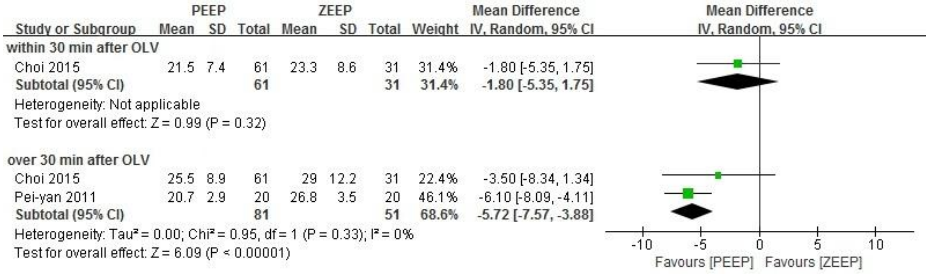


Figure 6. V_D/V_T within or over 30 min after onset of OLV

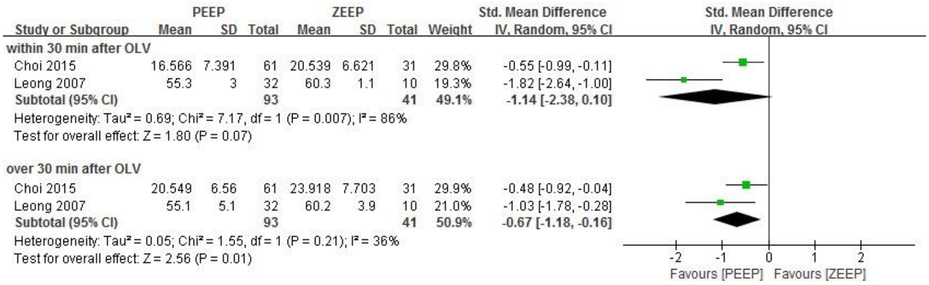


Figure 7. $P_{a\text{-}ET}CO_2$ gradient within or over 30 min after onset of OLV

Study or Subgroup	PEEP Mean	PEEP SD	PEEP Total	ZEEP Mean	ZEEP SD	ZEEP Total	Weight	Mean Difference IV, Random, 95% CI
within 30 min after OLV								
Choi 2015	5.922	2.383	61	7.398	1.939	31	28.4%	-1.48 [-2.38, -0.57]
Mascotto 2003	6.841	4.26	28	4.5	2.04	22	22.7%	2.34 [0.55, 4.13]
Subtotal (95% CI)			**89**			**53**	**51.1%**	**0.35 [-3.39, 4.09]**
Heterogeneity: Tau² = 6.76; Chi² = 13.85, df = 1 (P = 0.0002); I² = 93%								
Test for overall effect: Z = 0.18 (P = 0.85)								
over 30 min after OLV								
Choi 2015	7.417	2.102	61	8.317	2.194	31	28.3%	-0.90 [-1.84, 0.04]
Mascotto 2003	7.831	4.523	28	6.03	3.038	22	20.6%	1.80 [-0.30, 3.90]
Subtotal (95% CI)			**89**			**53**	**48.9%**	**0.28 [-2.35, 2.91]**
Heterogeneity: Tau² = 2.96; Chi² = 5.29, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 0.21 (P = 0.83)								

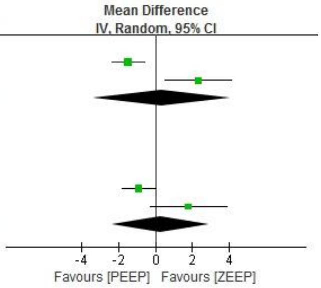


Figure 8. P/F ratio within or over 30 min after onset of OLV

Study or Subgroup	PEEP Mean	PEEP SD	PEEP Total	ZEEP Mean	ZEEP SD	ZEEP Total	Weight	Mean Difference IV, Random, 95% CI
within 30 min after OLV								
Choi 2015	267.1	66.3	61	284.5	67.3	31	11.7%	-17.40 [-46.35, 11.55]
Kim 2012	179.548	72.584	18	154.555	68.994	17	9.9%	24.99 [-21.91, 71.90]
Leong 2007	197.27	34.5	32	268.17	21.8	10	12.6%	-70.90 [-88.94, -52.86]
Mascotto 2003	147.044	47.213	28	174.487	70.575	22	11.2%	-27.44 [-61.73, 6.84]
Subtotal (95% CI)			**139**			**80**	**45.5%**	**-26.06 [-65.64, 13.53]**
Heterogeneity: Tau² = 1354.48; Chi² = 20.97, df = 3 (P = 0.0001); I² = 86%								
Test for overall effect: Z = 1.29 (P = 0.20)								
over 30 min after OLV								
Choi 2015	249.2	76.7	61	255.8	83.6	31	11.1%	-6.60 [-41.76, 28.56]
Kim 2012	157.185	68.504	18	157.185	49.794	17	10.7%	0.00 [-39.52, 39.52]
Leong 2007	211.89	50.67	32	230.02	35.08	10	11.8%	-18.13 [-46.08, 9.82]
Mascotto 2003	213.706	86.326	28	193.081	82.104	22	9.9%	20.63 [-26.27, 67.52]
Pei-yan 2011	372.6	56.7	20	304.2	63.1	20	10.9%	68.40 [31.22, 105.58]
Subtotal (95% CI)			**159**			**100**	**54.5%**	**11.73 [-19.53, 43.00]**
Heterogeneity: Tau² = 910.54; Chi² = 14.59, df = 4 (P = 0.006); I² = 73%								
Test for overall effect: Z = 0.74 (P = 0.46)								

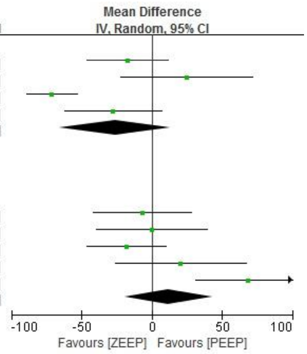


Figure 9. Vital signs within or over 30 min after onset of OLV

: Heart rate (HR), mean arterial pressure (MAP), and central venous pressure (CVP)

	PEEP			ZEEP				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
HR within 30 min								
Choi 2015	70	12.4	61	71	14	31	2.6%	-1.00 [-6.83, 4.83]
Kim 2012	85.86	12.056	18	87.975	10.623	17	1.5%	-2.11 [-9.63, 5.40]
Subtotal (95% CI)			**79**			**48**	**4.1%**	**-1.42 [-6.02, 3.19]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 0.60 (P = 0.55)								
HR over 30 min								
Choi 2015	70	10.7	61	69	10	31	4.5%	1.00 [-3.43, 5.43]
Kim 2012	85.78	13.328	18	86.795	10.765	17	1.4%	-1.02 [-9.02, 6.99]
Pei-yan 2011	82.2	7.4	20	81.3	6.3	20	4.8%	0.90 [-3.36, 5.16]
Subtotal (95% CI)			**99**			**68**	**10.6%**	**0.70 [-2.17, 3.56]**
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.90); I² = 0%								
Test for overall effect: Z = 0.48 (P = 0.63)								
MAP within 30 min								
Choi 2015	90.5	13.9	61	90	12	31	2.9%	0.50 [-4.98, 5.98]
Kim 2012	95.03	11.033	18	93.295	15.269	17	1.1%	1.73 [-7.13, 10.60]
Subtotal (95% CI)			**79**			**48**	**4.0%**	**0.84 [-3.82, 5.50]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.72)								
MAP over 30 min								
Choi 2015	87.5	10.9	61	86	11	31	3.9%	1.50 [-3.24, 6.24]
Kim 2012	86.195	9.395	18	86.29	9.043	17	2.3%	-0.10 [-6.20, 6.01]
Subtotal (95% CI)			**79**			**48**	**6.2%**	**0.90 [-2.84, 4.65]**
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%								
Test for overall effect: Z = 0.47 (P = 0.64)								
CVP within 30 min								
Choi 2015	17	3.5	61	16	3	31	46.3%	1.00 [-0.37, 2.37]
Subtotal (95% CI)			**61**			**31**	**46.3%**	**1.00 [-0.37, 2.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.43 (P = 0.15)								
CVP over 30 min								
Choi 2015	17	4.1	61	16	4	31	28.7%	1.00 [-0.74, 2.74]
Subtotal (95% CI)			**61**			**31**	**28.7%**	**1.00 [-0.74, 2.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.12 (P = 0.26)								

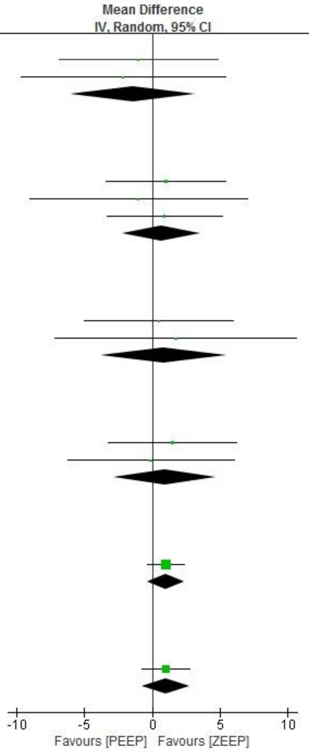


Figure 10. Airway pressure within or over 30 min after onset of OLV

: Peak airway pressure (P_{peak}), mean airway pressure (P_{mean}), and airway plateau pressure (P_{plat})

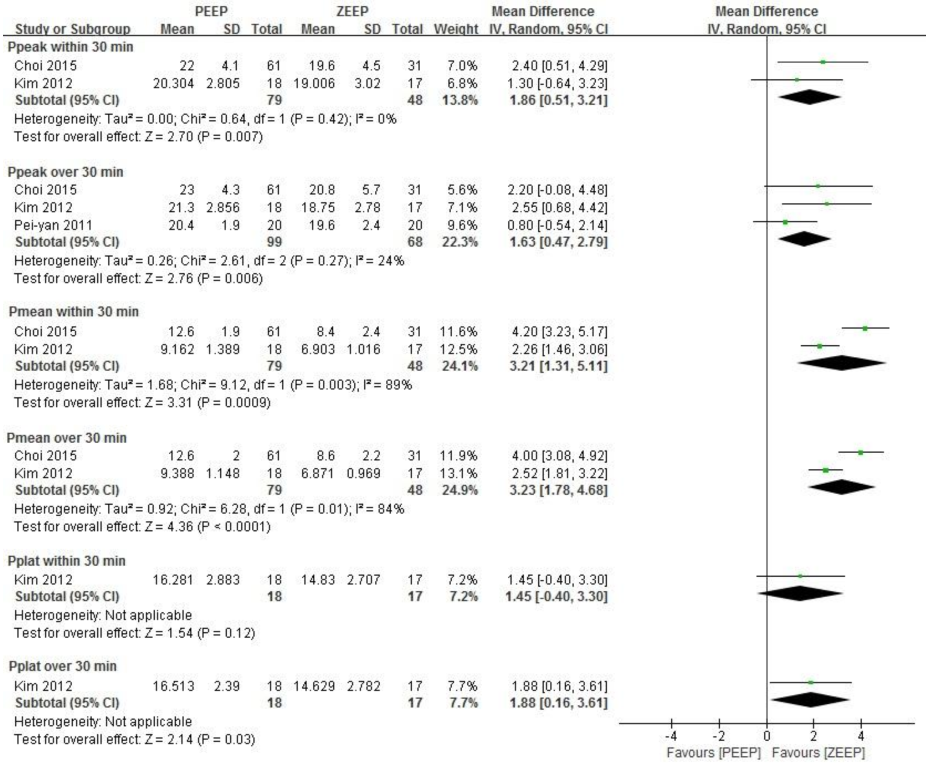
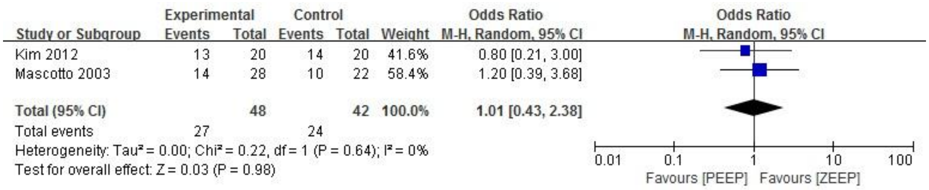


Figure 11. Desaturation event



Appendices

Strategies for searching eligible studies in each electronic database

MEDLINE

1. “one-lung ventilation”[mh] OR “thoracic surgery”[mh] OR “thoracic surgical procedures”[mh:noexp] OR “pulmonary surgical procedures”[mh:noexp] OR thoracotomy[mh] OR thoracoscopy[mh]
2. “one-lung ventilation”[tiab] OR “one-lung ventilations”[tiab] OR “single-lung ventilation”[tiab] OR “lung separation”[tiab]
3. (thoracic[tiab] OR thoracoscopic[tiab] OR pulmonary[tiab] OR chest[tiab] OR lung[tiab]) AND (surgery[tiab] OR surgeries[tiab] OR surgical[tiab] OR operation[tiab] OR operations[tiab] OR operative[tiab] OR resection[tiab] OR resections[tiab] OR lobectomy[tiab] OR bilobectomy[tiab] OR segmentectomy[tiab] OR metastasectomy[tiab])
4. 1 OR 2 OR 3
5. “positive-pressure respiration”[mh]
6. “positive end-expiratory pressure”[tiab] OR “positive end-expiratory pressures”[tiab] OR PEEP[tiab] OR PEEPs[tiab] OR ZEEP[tiab]
7. 5 OR 6
8. 4 AND 7
9. 8 & HSSS(S)

EMBASE

1. ‘one lung ventilation’/exp OR ‘thorax surgery’/exp OR ‘thoracoscopy’/exp
2. ’one-lung ventilation’:ab,ti OR ‘one-lung ventilations’:ab,ti OR ‘single-lung ventilation’:ab,ti OR ‘lung separation’:ab,ti
3. (thoracic:ab,ti OR thoracoscopic:ab,ti OR pulmonary:ab,ti OR chest:ab,ti OR lung:ab,ti) AND (surgery:ab,ti OR surgeries:ab,ti OR surgical:ab,ti OR

operation:ab,ti OR operations:ab,ti OR operative:ab,ti OR resection:ab,ti OR resections:ab,ti OR lobectomy:ab,ti OR bilobectomy:ab,ti OR segmentectomy:ab,ti OR metastasectomy:ab,ti)

4. #1 OR #2 OR #3
5. ’positive end expiratory pressure’/exp
6. ’positive end-expiratory pressures’:ab,ti OR PEEP:ab,ti OR PEEPs:ab,ti OR ZEEP:ab,ti
7. #5 OR #6
8. #4 AND #7
9. #8 & RCT filter
10. #9 AND [embase]/lim

CENTRAL

1. [mh “one-lung ventilation”] OR [mh “thoracic surgery”] OR [mh ^“thoracic surgical procedures”] OR [mh ^“pulmonary surgical procedures”] OR [mh “thoracotomy”] OR [mh “thoracoscopy”]
2. “one-lung ventilation”:ti,ab,kw OR “one-lung ventilations”:ti,ab,kw OR “single-lung ventilation”:ti,ab,kw OR “lung separation”:ti,ab,kw
3. (thoracic:ti,ab,kw OR thoracoscopic:ti,ab,kw OR pulmonary:ti,ab,kw OR chest:ti,ab,kw OR lung:ti,ab,kw) AND (surgery:ti,ab,kw OR surgeries:ti,ab,kw OR surgical:ti,ab,kw OR operation:ti,ab,kw OR operations:ti,ab,kw OR operative:ti,ab,kw OR resection:ti,ab,kw OR resections:ti,ab,kw OR lobectomy:ti,ab,kw OR bilobectomy:ti,ab,kw OR segmentectomy:ti,ab,kw OR metastasectomy:ti,ab,kw)
4. 1 OR 2 OR 3
5. [mh “positive-pressure respiration”]
6. ”positive end-expiratory pressure”:ti,ab,kw OR “positive end-expiratory pressures”:ti,ab,kw OR PEEP:ti,ab,kw OR PEEPs:ti,ab,kw OR ZEEP:ti,ab,kw 1659
7. 5 OR 6

8. 4 AND 7
9. 8 in trials

CINAHL

1. MH ("thoracic surgery" OR "surgery, lung+" OR "thoracostomy" OR "thoracotomy" OR "thoracoscopy")
2. TI ("one-lung ventilation" OR "one-lung ventilations" OR "single-lung ventilation" OR "lung separation") OR AB ("one-lung ventilation" OR "one-lung ventilations" OR "single-lung ventilation" OR "lung separation")
3. TI (thoracic OR thoracoscopic OR pulmonary OR chest OR lung) AND TI (surgery OR surgeries OR surgical OR operation OR operations OR operative OR resection OR resections OR lobectomy OR bilobectomy OR segmentectomy OR metastasectomy)
4. AB (thoracic OR thoracoscopic OR pulmonary OR chest OR lung) AND AB (surgery OR surgeries OR surgical OR operation OR operations OR operative OR resection OR resections OR lobectomy OR bilobectomy OR segmentectomy OR metastasectomy) 9972
5. 1 OR 2 OR 3 OR 4
6. MH ("positive end-expiratory pressure")
7. TI ("positive end-expiratory pressure" OR "positive end-expiratory pressures" OR PEEP OR PEEPs OR ZEEP) OR AB ("positive end-expiratory pressure" OR "positive end-expiratory pressures" OR PEEP OR PEEPs OR ZEEP)
8. 6 OR 7
9. 5 AND 8
10. 9 & RCT filter

Web of Science

1. one-lung ventilation OR thoracic surgery OR thoracic surgical procedures OR pulmonary surgical procedures OR thoracotomy OR thoracoscopy OR

one-lung ventilations OR single-lung ventilation OR lung separation

2. (thoracic OR thoracoscopic OR pulmonary OR chest OR lung) AND (surgery OR surgeries OR surgical OR operation OR operations OR operative OR resection OR resections OR lobectomy OR bilobectomy OR segmentectomy OR metastasectomy)
3. 1 OR 2
4. positive end-expiratory pressure OR positive end-expiratory pressures OR PEEP OR PEEPs OR ZEEP
5. 3 AND 4
6. 5 AND RCT filter

Scopus

1. INDEXTERMS(one-lung ventilation) OR INDEXTERMS(thoracic surgery) OR INDEXTERMS(thoracic surgical procedures) OR INDEXTERMS(pulmonary surgical procedures) OR INDEXTERMS(thoracotomy) OR INDEXTERMS(thoracoscopy)
2. TITLE-ABS(one-lung ventilation) OR TITLE-ABS(one-lung ventilations) OR TITLE-ABS(single-lung ventilation) OR TITLE-ABS(lung separation)
3. (TITLE-ABS(thoracic) OR TITLE-ABS(thoracoscopic) OR TITLE-ABS(pulmonary) OR TITLE-ABS(chest) OR TITLE-ABS(lung)) AND (TITLE-ABS(surgery) OR TITLE-ABS(surgeries) OR TITLE-ABS(surgical) OR TITLE-ABS(operation) OR TITLE-ABS(operations) OR TITLE-ABS(operative) OR TITLE-ABS(resection) OR TITLE-ABS(resections) OR TITLE-ABS(lobectomy) OR TITLE-ABS(bilobectomy) OR TITLE-ABS(segmentectomy) OR TITLE-ABS(metastasectomy))
4. 1 OR 2 OR 3
5. INDEXTERMS(positive end expiratory pressure)
6. TITLE-ABS(positive end-expiratory pressure) OR TITLE-ABS(positive end-expiratory pressures) OR TITLE-ABS(PEEP) OR TITLE-ABS(PEEPs)

OR TITLE-ABS(ZEEP)

7. 5 OR 6
8. 4 AND 7
9. 8 & RCT filter

KoreaMed

"Positive-Pressure Respiration" [MH] OR "positive end-expiratory pressure" [TI] OR "positive end-expiratory pressure" [AB] OR PEEP [TI] OR PEEP [AB] OR PEEPs [TI] OR PEEPs [AB]

국문 초록

서론: 호기말양압은 일측폐환기 중 발생한 저산소증의 대응전략으로 흔히 사용된다. 하지만 일측폐환기 상황에서 산소화에 대한 호기말양압의 효용에 대해서는 논란이 있다. 이에 일측폐환기 중 호기말양압의 영향에 대한 무작위배정비교임상시험의 체계적 문헌고찰과 메타연구를 시행하였다.

연구방법: CENTRAL, CINHAL, EMBASE, MEDLINE, SCOPUS, Web of Science, KoreaMed 를 포함한 데이터베이스에서 계통적인 문헌검색을 시행하였으며 최종적으로 525 명의 대상자를 포함한 7 개의 무작위배정비교임상시험을 선택하여 체계적 문헌고찰과 메타분석을 시행하였다. 주요결과변수로는 기체교환효율을 반영하는 혈중산소량 대 흡입산소분율 비율의 변화를, 보조결과변수로 폐유순도, 사강 대 호흡량 비율, 단락율, 동맥혈과 호기말 이산화탄소 분압차, 일측폐환기 중 저산소증 발생여부, 회복실에서의 수술 후 폐합병증의 영상의학적 평가, 수술 후 폐기능검사 결과 등의 지표를 관찰하였다. 주요결과변수에 대해 표준화 평균차(standardized mean difference, SMD)와 95% 신뢰구간(confidence interval, CI)을, 보조결과변수에 대해 평균차(mean difference, MD)와 95% 신뢰구간을 계산하였으며 필요할 경우 하위그룹분석을 통해 이질성의 근원을 평가하였다.

결과: 폐유순도는 일측폐환기시작 후 30 분 경과 이전과 이후 모두

증가하는 양상을 보였으나 통계적으로 유의하지 않았다[30 분 경과 이전: SMD (95% CI) = 0.50 (−0.10, 1.10), P = 0.10, I^2 = 80%, 30 분 경과 이후: SMD (95% CI) = 0.51 (−0.04, 1.06), P = 0.07, I^2 = 71%]. 단락율은 일측폐환기 시작 30 분 경과 이후부터는 호기말양압 군에서 유의하게 낮았다[MD (95% CI) = −5.72 (−7.57, −3.88), P < 0.001]. 폐사강대 호흡량의 비율은 일측폐환기 시작 후 30 분 경과 이전에는 호기말양압군에서 낮은 모습을 보였으나 통계적으로 유의하지는 않았다[SMD (95% CI) = −1.14 (−2.38, 0.10), P = 0.07]. 하지만 일측폐환기 30 분 경과 이후에는 호기말양압군에서 폐사강 대 호흡량 비율이 유의하게 낮은 결과가 도출되었다[SMD (95% CI) = −0.67 (−1.18, −0.16), P = 0.01]. 동맥혈과 호기말 이산화탄소 분압차는 포함된 연구 사이에 이질적인 결과가 관찰되었다. 하지만 산소화 능력은 PEEP 에 의해 감소하는 양상을 보였다. 일측폐환기 시작 후 30 분 경과 이전에는 동맥혈중산소량 대 흡입산소분율의 비율이 감소하는 양상을 보였다[MD (95% CI) = −26.06 (−65.64, 13.53), P = 0.20, I^2 = 86%]. 30 분경과 이후에는 양 군 사이에 유의한 차이가 관찰되지 않았다[MD (95% CI) = 11.73 (−19.53, 43.00), P = 0.46, I^2 = 73%]. 일측폐환기 중 저산소증발생은 양 군 간에 차이가 없었다[OR (95% CI)=−1.01 (0.43, 2.38), P = 0.98, I^2 = 0%]. 수술 후 72 시간째의 폐기능 검사결과는 호기말양압군에서 유의하게 좋았다. 수술 후 무기폐의 발생은 양 군간 차이가 없었다.

결론: 이 메타분석을 통해 일측폐환기 중 적용하는 호기말양압이

일측폐환기 적용 30분 경과 후의 폐단락율과 폐사강대 호흡량 비율을 개선하지만 이것이 산소화 능력의 향상으로 연결되지 않는다는 것을 발견할 수 있었다. 산소화에 관한 명확한 증거가 발견되지 않았으므로, 일측폐환기 중 발생한 저산소혈증에 대해 호기말양압을 적용할 때 세심한 주의가 필요할 것이다.

주요어: 호기말양압, 양압환기, 흉부수술

학번: 2015-23231